08/974,186 11/19/97 BOYLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231 A-378D5

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
		HM31/0717	

U.S. PATENT DEPARTMENT/RBW
AMGEN, INC
AMGEN CENTER, M/S 10-1-B
1840 DE HAVILLAND DRIVE
THOUSAND OAKS CA 91320-1789

CAMPELL, B

EXAMINER
1632

ART UNIT	PAPER NUMBER
07/17/98	

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
8/974,186	Boyle et al
Examiner	**Group Art Unit**
Campell	1632

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to preliminary communication(s) filed on 11/19/97.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 45-48 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☑ Claim(s) 45-48 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☑ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☑ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

The preliminary amendment filed November 19, 1997 has been entered.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The specification does not include a sequence listing in paper form or in computer readable form (CRF). Applicants may use the CRF from the parent application by submitting a request under 37 CFR 1.821(e), but a new paper form is required for this application. Also, the application must refer to the SEQ ID No. every time a sequence is cited in the specification, drawings and claims (37 CFR 1.821(d)).

Applicants must comply with the sequence rules for the response to this Office action to be complete.

Applicants must amend the specification at pages 10 and 11 to either provide the deposit information or delete the blank spaces. A blank space also appears at p. 14 of the specification. This space should be deleted unless Applicants can show that filling in the blank would not introduce new matter.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and state of the prior art. The claimed invention consists of methods of treating bone loss by gene therapy. At the time the parent application was filed, successful use of gene therapy was not routinely obtainable by those skilled in the art. One important obstacle is the inability to

achieve a high level of expression of the introduced gene for a prolonged period of time. For example, Marshall states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col. 3). James Wilson, one skilled in the art, is quoted as saying that "'[t]he actual vectors - how we're going to practice our trade - haven't been discovered' yet" (p. 1055, col. 2). Culver et al., reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge" (p. 178). Hodgson discusses the drawbacks of viral transduction and chemical transfection methods, and states that "[d]eveloping the techniques used in animal models, for therapeutic use in human somatic cells, has not been straightforward" (pp. 459-460). Miller et al. also review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances....targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col. 1). The specification does not address the problems discussed above.

The physiology of bone formation and resorption is complex and poorly understood. For example, Siddhanti et al. teach that osteoblast proliferation and differentiation are controlled by a "multitude of systemic and local factors" and "various signal transduction pathways" (paragraph bridging pp. 310-311). Siddhanti et al. present a model of osteoblast growth and development in which tyrosine kinases are one of many factors controlling these processes (Fig. 2), and conclude that "the final outcome of transcriptional regulation of osteoblast function results from complex interactions between signaling pathways and permissive differentiating transcription factors" (abstract). Similarly, Mundy et al. state, "There are numerous signals at resorption sites which could be responsible for the cessation of osteoclast activity" (p.

72S, col. 1). Mundy et al. conclude that "agents which increase bone formation are sorely needed for the treatment of osteoporosis....One of the major challenges for bone cell biologists in this area is to understand how these multiple growth regulatory factors interact in their effects on bone" (p. 74S). The specification indicates that the cause(s) of bone loss are unknown (p. 20, lines 28-29). Taken together, the evidence above establishes that the art is extremely complex and poorly understood.

Predictability of the art. The physiological art is recognized as unpredictable (MPEP 2164.03). The specification describes the effect of constitutively overexpressing osteoprotegerin in otherwise normal transgenic mice, but there is no evidence on the record that relates this effect to gene therapy of subjects suffering from bone loss. The pathways controlling bone formation and resorption are complex, as described above. There is no way to predict whether any one of the processes causing bone loss (hormonal changes in osteoporosis, infection in osteomyelitis, cancer, etc.) could be reversed (temporarily or permanently) by expressing osteoprotegerin.

Guidance and working examples. The specification provides no guidance for practice of the claimed methods except to state that the disclosed nucleic acids should be administered. No working examples are provided.

Breadth of the claims. The claims are extremely broad, encompassing treatment of bone loss resulting from any disease state using any type of vector.

Amount of experimentation necessary. Given the state of the art as described above, it would likely require considerable experimentation to develop a method for treating bone loss by gene therapy.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods. This is particularly true given the nature of the invention, the state of the art, the breadth of the claims, the amount of experimentation necessary, the scarcity of guidance and absence of working examples in the specification, and the unpredictable nature of the art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce Campell, whose telephone number is 703-308-4205. The examiner can normally be reached on Monday-Thursday from 8:00 to 4:30 (Eastern time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-305-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Bruce Campell

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800